(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2003 (12.09.2003)

PCT

(10) International Publication Number
WO 03/074074 A1

(51) International Patent Classification[7]: A61K 38/17

(21) International Application Number: PCT/KR03/00419

(22) International Filing Date: 5 March 2003 (05.03.2003)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
10-2002-0011500 5 March 2002 (05.03.2002) KR

(71) Applicant *(for all designated States except US)*: **ANGIO-LAB, INC.** [KR/KR]; Bio-Med RRC, Pai Chai University, 439-6, Doma-2dong, Seo-gu, Taejon 302-735 (KR).

(71) Applicant and
(72) Inventor: **KIM, Min-Young** [KR/KR]; 111-801, Samsung Pureun Apt., Jeonmin-dong, Yoosung-gu, Taejon 305-727 (KR).

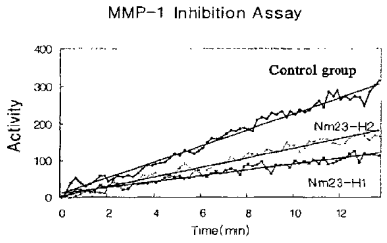
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LEE, Kong-Joo** [KR/KR]; 230-404, Sinsigaji Apt., Mok-6dong, Yangcheon-gu, Seoul 158-056 (KR). **KIM, Eun-hee** [KR/KR]; 109-1004, Expo Apt., Jeonmin-dong, Yoosung-gu, Taejon 305-390 (KR). **PARK, Byung-Young** [KR/KR]; 104-902, Parangsae Apt., Dunsan-dong, Seo-gu, Taejon 302-774 (KR).

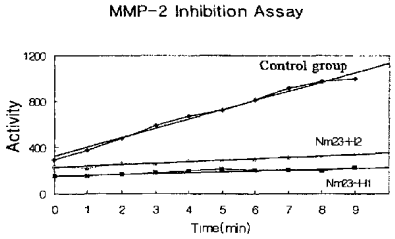
(74) Agents: **PARK, Seung-Moon** et al.; DARAE Law & International Patent, 18th Floor, Kangnam Building, 1321-1, Seocho-dong, Seocho-ku, Seoul 137-070 (KR).

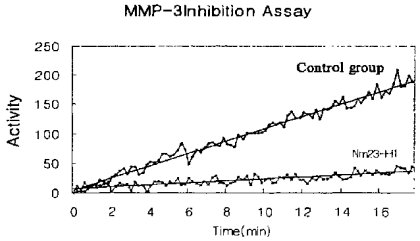
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG,

[Continued on next page]

(54) Title: COMPOSITIONS COMPRISING Nm23 PROTEIN FOR THE USE OF MATRIX METALLOPROTEINASE INHIBITOR AND ANGIOGENESIS INHIBITOR







(57) Abstract: The present invention relates to a pharmaceutical compositions comprising Nm23 as an active ingredient for inhibiting MMP activity and angiogenesis. The pharmaceutical formulations comprising Nm23 can be used as a drug for prevention and treatment of wide-ranging diseases mediated by overactivity of MMP and/or abnormal angiogenesis.

WO 03/074074 A1

SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Compositions comprising Nm23 protein for the use of matrix metalloproteinase inhibitor and angiogenesis inhibitor

Background of Invention

Technical Field

The present invention relates to pharmaceutical compositions for the use of matrix metalloproteinase (MMP) inhibitor and angiogenesis inhibitor comprising Nm23 protein as an active ingredient.

Background Art

Angiogenesis is the process of forming new capillary blood vessels from microvessels. Angiogenesis occurs only during embryonic development, wound healing and female cyclic menstruation with the corpus luteum, but not under normal conditions [Folkman and Cotran, Regulation of proliferation to tumor growth. *Int. Rev. Exp. Pathol.* 16:207-248, 1976].

A failure in the regulation of angiogenesis can lead to the following disorders: angioma; angiofibroma; blood vessel malformation; cardiovascular diseases such as arteriosclerosis, intravascular coagulation and edematous sclerosis; ophthalmological diseases such as cornea-implant angiogenesis, neovascular glaucoma, diabetic retinopathy, corneal disorder; involutional macula, pterygium, degeneration of macula, retrolental fibroplasias and granula trachoma; chronic inflammatory diseases such as arthritis; and skin disorders such as the psoriasis, capillary extension, the pyogenic granuloma, seborrheic dermatitis and acne. Angiogenesis plays very important role in growth and metastasis of cancer cells

[D'Amato RJ and Adamis AP, *Ophthamol* 102:1261-1262, 1995; Arbiser JL, *J. Am. Acad. Derm.* 34(3): 486-497, 1996; O'brien KD. et al. *Circulation* 93(4): 672-682, 1996; Hanahan D and Folkman *J. Cell.* 86:353-364, 1996].

Angiogenesis influences growth and proliferation of cancer by supplying nutrients and oxygen, and also promotes for the metastasis of cancer cells to the circulating system of the blood and thus to the other parts of the entire body through neovascularization [Polverini PJ. *Critical Reviews in Oral Biology*, 6(3): 230-247, 1995].

Abnormal angiogenesis thus underlies the origin and progression of a number of diseases. Development of effective inhibitors of angiogenesis is important for the prevention and treatment of such diseases and is currently an active area of research.

A major event that occurs during angiogenesis, prior to the formation of the capillary blood vessels, is the breakdown of extracellular matrix. Other key steps in the angiogenic cascade include reactivation of endothelial cells, rupture of membrane, adhesion, migration, proliferation, lumen formation, and sprouting off new capillary blood vessels out of preexisting vessels. The most important enzymes in degradation of the extracellular matrix (collagen type IV, a main component of the basement membrane), is matrix metalloproteinases (MMPs), a family of over 20 enzymes.

MMPs are endopeptidases containing zinc (Zn), which degrade extracellular matrix such as connective tissue and basement membrane. They are classified into four groups: collagenase (e.g. MMP-1, MMP-8), gelatinase (e.g. MMP-2, MMP-9), stromelysin (e.g. MMP-3), and membrane-type collagenase (e.g. MMP-14). Collagenase participates in bone-arthritis while gellatinase plays a role in growth and metastasis of cancer by degrading the basement membrane [Howell DS and Pelaetier

JP. In Arthritis and Allied Conditions; McCarthy DJ and Koopman WJ. Eds; Lea and Febiger; Philadelphia, 12th Ed. 2:1723, 1993].

MMPs are also involved in the development of many other diseases from overactivation of MMP, among them, re-stenosis, osteo-hypotropy, inflammatory disorders in CNS, skin diseases of aging such as wrinkles; dermatitis, rheumatoid arthritis, septicemia arthritis, corneal ulcer, abnormal wound healing, bone diseases, proteinuria, aneurysm, degenerative cartilage loss caused by traumatic articular injury, demyelinating disease in nervous system, cirrhosis of the liver, glomerular disease, embryonic membrane rupture, inflammatory bowel disease, periodontal membrane disease, age-related degeneration of macula, diabetic retinopathy, proliferated retina syndrome, premature infant's retinopathy, ophthalmia, cone cornea, Shogren's syndrome, myopia, and ophthalmo-tumor. MMPs are also involved in the rejection of corneal graft.

There is, therefore, an urgent need for effective, non-toxic inhibitors of angiogenesis and metalloproteinases as potential to therapeutic agents for a variety of diseases.

Several lines of evidence suggest that Nm23, an endogenous protein, has nucleoside diphosphate kinase (NDPK) activity [Biggs et al., A Drosphilia gene that is homologous to a mammalian gene associated with tumor metastasis codes for a nucleoside diphospahte kinase. *Cell*, 63:933-940, 1990]. Also, Nm23 has been shown to serve as a transcriptional factor, and cell differentiation inhibitor [Postel et al, Human c-myc transcription factor PuF identified as Nm23-H2 nucleoside diphosphate kinase, a candidate suprpressor of tumor metastasis. *Science*. 261:478-480, 1993; Okabe-kado et al., Inhibotory action of Nm23 proteins on erythroid differentiation of human leukemia cells. *Biochem. Biophys. Acta*. 1267: 101-106,

1995].

This inhibitory activity is shared by both the acidic Nm23-H1 isoform and the basic Nm23-H2 isoform in human, and both types were shown to inhibit cell invasion and metastasis [Rosengard et al: Reduced Nm23/Awd protein in tumor metastasis and aberrant Drosphilia development. *Nature*, 342:177-180, 1989; Charpin et al: Automated and quantitative immunocytochemical assays of Nm23/NDPK protein in breast carcinomas, *Int. J. Cancer*, 74:416-420, 1997].

However, the mechanisms of action of Nm23 has not well understood, though its activities and effects as described above have been shown. Therefore, this protein has a limit in application and there is a need for clarifying the working mechanism of Nm23 so as to provide applicability in various diseases. Also, there is a great need for development of a drug effective in the prevention and treatment of many diseases induced by overexpression of MMP and abnormal angiogenesis.

The present inventors have studied the relationship between NM23 and the activity of MMP and angiogenesis to provide an effective composition for prevention and treatment of many diseases induced by overexpression of MMP and abnormal angiogenesis.

Detailed Description of Invention

The present invention provides compositions comprising Nm23 as an active ingredient for inhibiting the matrix metalloproteinase (MMP) activity and angiogenesis.

It is a further object of the present invention to provide a composition for prevention and treatment of MMP-mediated diseases, such as re-stenosis, MMP-mediated osteo-hypotropy, inflammatory disorders in CNS, skin aging, wrinkles,

dermatitis, rheumatoid arthritis, septicemia arthritis, corneal ulcer, abnormal wound healing, bone disease, proteinuria, aneurysm disease, degenerative cartilage loss caused by traumatic articular injury, demyelinating disease in nervous system, cirrhosis of the liver, glomerular disease, embryonic membrane premature rupture, inflammatory bowel disease, periodontal membrane disease, age-related degeneration of macula, diabetic retinopathy, proliferated retina syndrome, premature infant's retinopathy, ophthalmia, cone cornea, Shogren's syndrome, myopia, ophthalmo-tumor, the rejection of corneal graft, and the like, comprising Nm23 as an active ingredient.

It is another object of the present invention to provide a composition for inhibiting angiogenesis activity comprising Nm23 as an active ingredient.

It is yet another object of the present invention to provide a composition for prevention and treatment of angiogenesis-related diseases, such as angioma, angiofibroma, diabetic retinopathy, premature infant's retinopathy, neovascular glaucoma, angiogenesis-related corneal disorder; involutional macula, pterygium, degeneration of macula, retrolental fibroplasias, granula trachoma, psoriasis, capillary extension, pyogenic granuloma, seborrheic dermatitis, fatness, acne and arthritis, comprising Nm23 as an active ingredient.

The term Nm23 protein used herein includes all proteins containing amino acids encoded by the human Nm23 genes (US PAT. NO. 6,329,198), and derivatives and fragments thereof and showing the same functions.

The Nm23 protein used herein includes Nm23 proteins encoded by the human Nm23-H1 genes and the human Nm23-H2 genes, and derivatives and fragments thereof and showing the same functions.

The Nm23 protein used herein applies to all forms of Nm23 protein whether

obtained from natural sources or artificially prepared using a peptide synthesizer or by a genetic engineering.

The Nm23 protein used herein may be mass-produced by *E. coli*. In this case, the product is preferably purified by ATP-sepharose column chromatography.

The present invention covers all compositions comprising proteins showing the same functions as human Nm23 protein, and derivatives and fragments thereof as an active ingredient alone.

The present invention covers all compositions comprising proteins showing the same functions as human Nm23 protein, and derivatives and fragments thereof as an active ingredient in combination with another active ingredient.

For administration, the compositions comprising Nm23 according to the present invention may include at least one other pharmaceutically acceptable carrier.

The pharmaceutically acceptable carrier suitable for liquid formulation may include saline, sterile water, Ringer's solution, buffered saline, dextrose solution, malto dextrin solution, glycerol, ethanol or a mixture of one or more these and may be combined with other common additives, including, for example, anti-oxidants, a buffer solution, bacteriostatic agents and the like, as needed. Also, the active agent may be formulated as an injectible form (aqueous solution, suspension, emulsion and the like), a pill, a capsule, granule or tablet, by adding a diluting agent, a dispersing agent, a surfactant, a binder or a lubricant. Further, it may be variably formulated according to the diseases to be treated or prevented, by appropriate methods described in Remington's Pharmaceutical Science, Mack Publishing Company, Easton PA.

The formulation resulting from this invention may be administered by the intravenous (IV), intraperitoneal (IP), intramuscular (IM), intraarterial (IA),

transdermal, intranasal, inspiration, focal, rectal, oral, intraocular or intradermal routes. Among them, parenteral administration includes the intraveneous, intramuscular, intraperitoneal, intrasternal, transdermal and intraarterial injection and infusion.

An effective dose is preferably 0.05mg to 2g per a day, which may be administered all at once or in several smaller doses depending, among others, on the type of the disease to be treated or prevented, the types and contents of an active ingredient and the other ingredients contained in the formulation, the route, and duration of administration, the age, body weight, general health condition, sex and diet of the patient, duration of the treatment, co-treatment drug (for example, chemotherapeutics).

The composition described in the present invention has been confirmed to strongly inhibit MMP activity in a spectrofluorometric MMPinhibition assay.

Also the composition described in the present invention has been confirmed to strongly inhibit angiogenesis in endothelial cells in a tube formation assay using a gelled Matrigel and an animal test using a mouse Matrigel model.

Brief Description of the Drawings

Fig. 1: Inhibition of MMP activity by Nm23-H1 and Nm23-H2;

Fig. 2: Tube formation in the HUVEC (Human umbilical vein endothelial cell);

Fig. 3: Inhibitory effect of Nm23-H1 on the tube formation in endothelial cells on Matrigel;

Fig. 4: Inhibitory effect of Nm23-H2 on the tube formation in endothelial cells on Matrigel; and

Fig. 5: Inhibitory effect of Nm23-H1 and Nm23-H2 on angiogenesis in a mouse Matrigel model.

Best Mode for Carrying Out the Invention

The following examples help to understand the present invention. However, the present invention is not limited to these examples.

Preparation Example: Preparation of Nm23-H1 and Nm23-H2

Nm23-H1 and Nm23-H2 were recombinant proteins which were prepared following their over-expression in *E. coli,* and purification to at least 99% purity by ATP-sepharose affinity column chromatography [Kim et al., *Mol. Cell,* 7:630-634, 1997]. The recombinant proteins thus obtained were confirmed to be identical in structure with naturally existing Nm23 protein.

Example 1: Inhibitory Effect of Nm 23 on MMP Activity

The Inhibiting effect of Nm23 on MMP activity was examined using a spectrofluorometer (Perkin-Elmer, LS50B). MMPs were prepared from insect cells using the Baculovirus system by the genetic engineering technique.

Substrates for MMPs are as follows; 2,4-dinitrophenyl-Pro-Leu-Ala-Leu-Trp-Ala-Arg (Calbiochem, San Diego, CA, No.444211) as substrate for MMP-1; 2,4-dinitrophenyl-Pro-Leu-Gly-Met-Trp-Ser-Arg (Calbiochem, San Diego, CA, No. 444215) as substrate for MMP-2 and MMP-9; and 2,4-dinitrophenyl-Pro-Tyr-Ala-Tyr-Trp-Met-Arg (Calbiochem, San Diego, CA, No.444220) as substrate for MMP-3.

Fluorescence was measured at an excitation wavelength of 280 nm and an emission of 360nm.

Figure 1 shows that Nm23-H1 inhibited MMP-1 by 63%, MMP-2 by 90% and MMP-3 by 82%, and Nm23-H2 inhibited MMP-1 by 40% and MMP-2 by 84%, in the concentration of 2㎍/㎖, as compared with the control group.

Example 2: Inhibitory Effect of Nm23 on angiogenesis *in vitro*.

The effect of Nm23 on the capillary vessel formation in human vascular endothelial cells, *in vitro* was examined as follows. Human umbilical vein endothelial cells (HUVEC) were isolated from fresh human umbilical cord obtained from a caesarean operation and cultured in media. Their identity was confirmed by immunostaining with antibody against factor VIII. The HUVE cells were grown in gelled Matrigel supplied by Collaborative Biomedical Products at 37℃ for 16 to 18 hours. The HUVE cells thus obtained were the control group.

HUVE cells further treated with Nm23 at a concentration of 125 ㎍/㎖ were compared with the control group.

Fig. 2 shows the reticular tube formation by the HUVE cells cultured on Matrigel, which appeared as a stage of the angiogenesis.

Fig. 3 shows that reticular tube formation is interrupted in HUVE cells cultured on Matrigel, after treatment with Nm23-H1 at a concentration of 125 ㎍/㎖.

Fig. 4 shows that reticular tube formation is interrupted in the HUVE cells cultured on Matrigel, after treatment with Nm23-H2 at a concentration of 125 ㎍/㎖.

The area of the tubes formed on Matrigel was analyzed using the Image-Pro Plus, supplied by Media Cybernetics. Table 1 shows Nm23-H1 and Nm23-H2 inhibited the tube formation by about 41% and 45%, respectively.

<Table 1>

	Area of Tubes	Tube Formation (%)
Control Group	92	100
Nm23-H1-treated	54	59
Nm23-H2 treated	51	55

Example 3: Inhibitory Effect of Nm23 on angiogenesis *in vivo*.

The inhibitory effects of Nm23-H1 and Nm23-H2 on angiogenesis were examined using the mouse Matrigel model.

6 to 8 weeks old C57BL/6 mice were injected subcutaneously with a mixture of 0.4 ㎖ of Matrigel (Collaborative Biomedical Products), 50 ng/㎖ of fibroblast growth factor(FGF), an angiogenesis inducing factor, and 50 units/㎖ of heparin to induce angiogenesis (control group). After 3 - 5 days, the skin of each animal was removed and Matrigel was carefully separated, followed by recovery of gel. The amount of hemoglobin was measured using Drabkin's reagent (Sigma). 49 ㎍ of Nm23-H1 and Nm23-H2 were added to Matrigel and administered to animals, as described above. Matrigel plugs were removed and the amount of hemoglobin was measured by Drabkin's reagent kit 525 (Sigma, St. Louis, MO).

As shown in Table 2 and Fig. 5., Nm23-H1 and Nm23-H2 inhibited angiogenesis by 74% and 77%, respectively.

<Table 2>

	Conc. of Hb (g/dℓ)	Inhibition of Angiogenesis (%)
Control Group	390± 254	0
Nm23-H1-treated Group	102± 134	74
Nm23-H2 treated Group	91± 96	77

Industrial Applicability

The compositions described in this invention, comprising Nm23 as the active ingredient have inhibitory effect on MMP activity and hence have potential therapeutic use in the prevention and treatment of various conditions and diseases resulting from overexpression of MMP.

They are also potentially effective in the prevention and treatment of various conditions and diseases induced by abnormal angiogenesis.

What is claimed is:

1. A pharmaceutical composition for inhibiting MMP activity which comprises Nm23 as an active ingredient.

2. The pharmaceutical composition of claim 1, in which said Nm23 is Nm23-H1.

3. The pharmaceutical composition of claim 1, in which said Nm23 is Nm23-H2.

4. The pharmaceutical composition of any one of claims 1 to 3, are potentially useful for the prevention and treatment of re-stenosis, MMP-mediated osteo-hypotropy, inflammatory disorders in CNS, skin aging, wrinkles, dermatitis, rheumatoid arthritis, septicemia arthritis, corneal ulcer, abnormal wound healing, bone disease, proteinuria, aneurysm disease, degenerative cartilage loss caused by traumatic articular injury, demyelinating disease in nervous system, cirrhosis of the liver, glomerular disease, embryonic membrane rupture, inflammatory bowel disease, periodontal membrane disease, age-related degeneration of macula, diabetic retinopathy, proliferated retina syndrome, premature infant's retinopathy, ophthalmia, cone cornea, Shogren's syndrome, myopia, ophthalmo-tumor, the rejection of corneal graft, and the like.

5. The pharmaceutical composition of claim 4, in which the composition is formulated into any one selected from the group consisting of injections, inhalants, sprays, tablets, capsules, soft capsules, solutions, granules, pills and ointments.

6. A pharmaceutical composition for inhibiting angiogenesis which comprises Nm23 as an active ingredient.

7. The pharmaceutical composition of claim 6, in which said Nm23 is Nm23-H1.

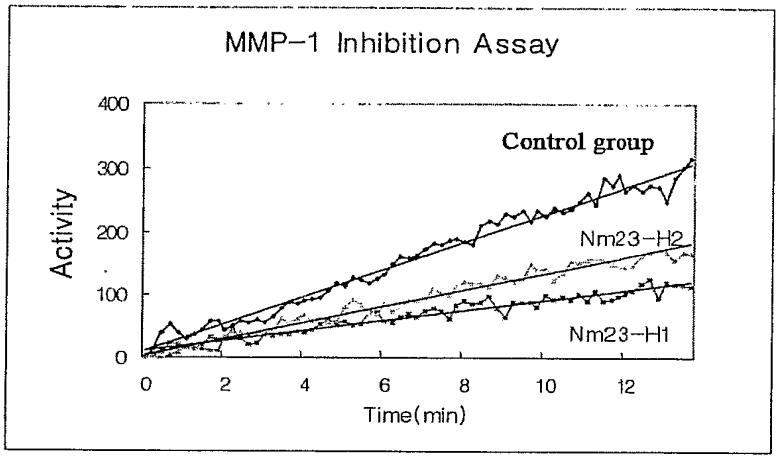
8. The pharmaceutical composition of claim 6, in which said Nm23 is Nm23-H2.

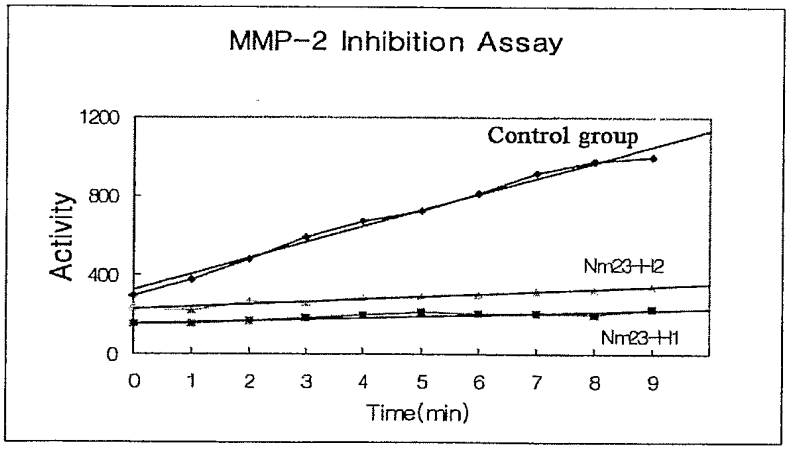
9. The pharmaceutical composition of any one of claims 6 to 8, are potentially useful for the prevention and treatment of angioma, angiofibroma, diabetic retinopathy, premature infant's retinopathy, neovascular glaucoma, angiogenesis-related corneal disorder; involutional macula, degeneration of macula, pterygium, retinal degeneration, retrolental fibroplasias, granula trachoma, psoriasis, capillary extension, pyogenic granuloma, seborrheic dermatitis, acne, fatness and arthritis.

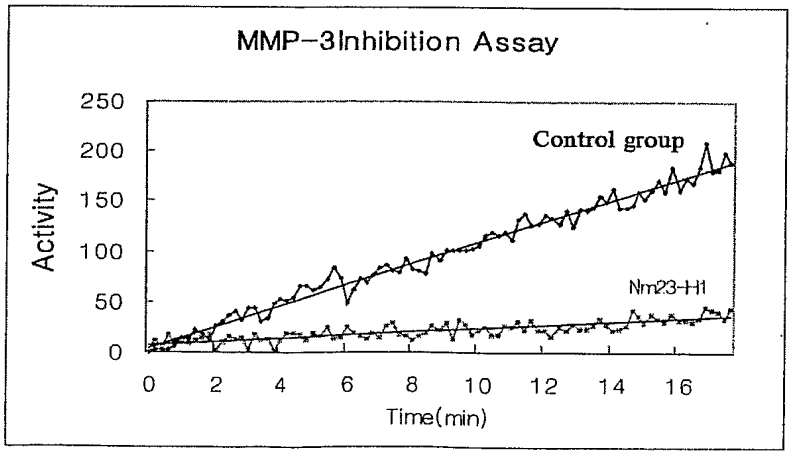
10. The pharmaceutical composition of claim 9, in which the composition is formulated into any one selected from the group consisting of injections, inhalants, sprays, tablets, capsules, soft capsules, solutions, granules, pills and ointments.

[DRAWING]

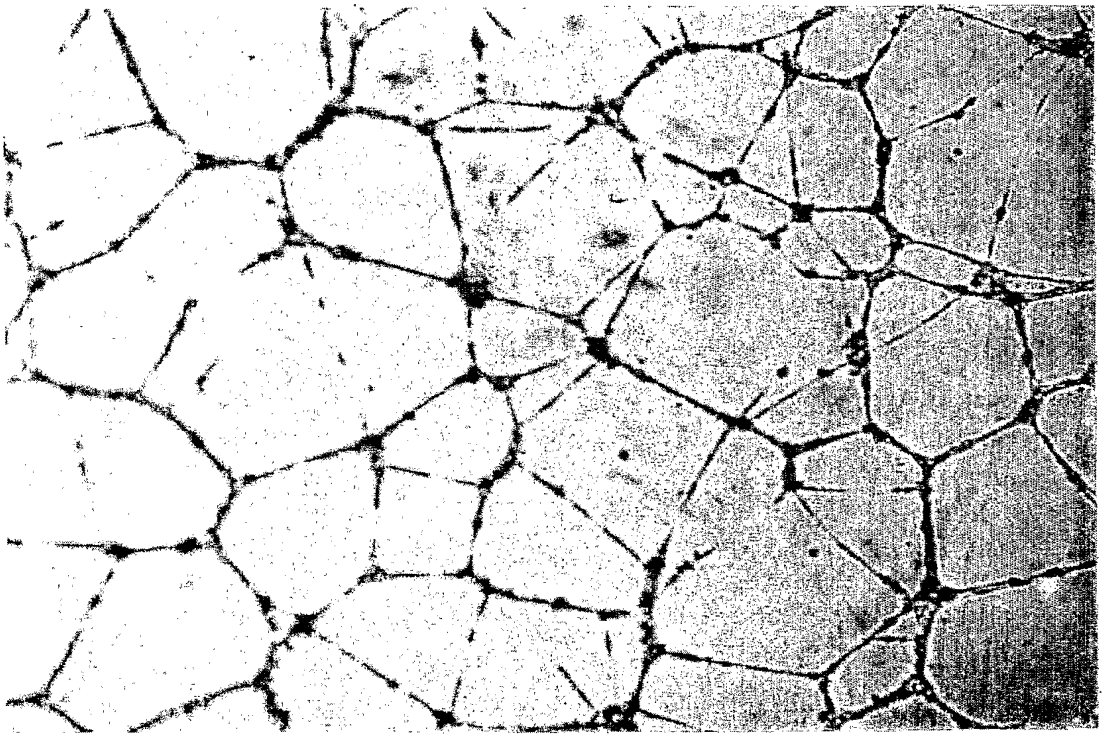
[FIG. 1]



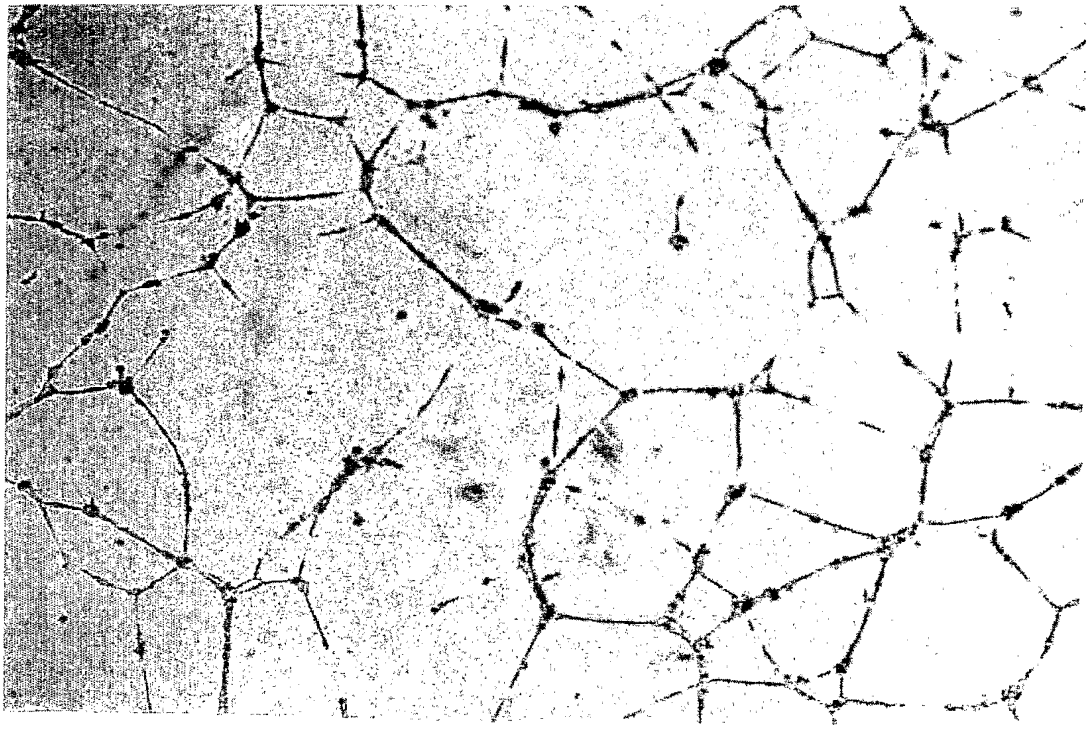




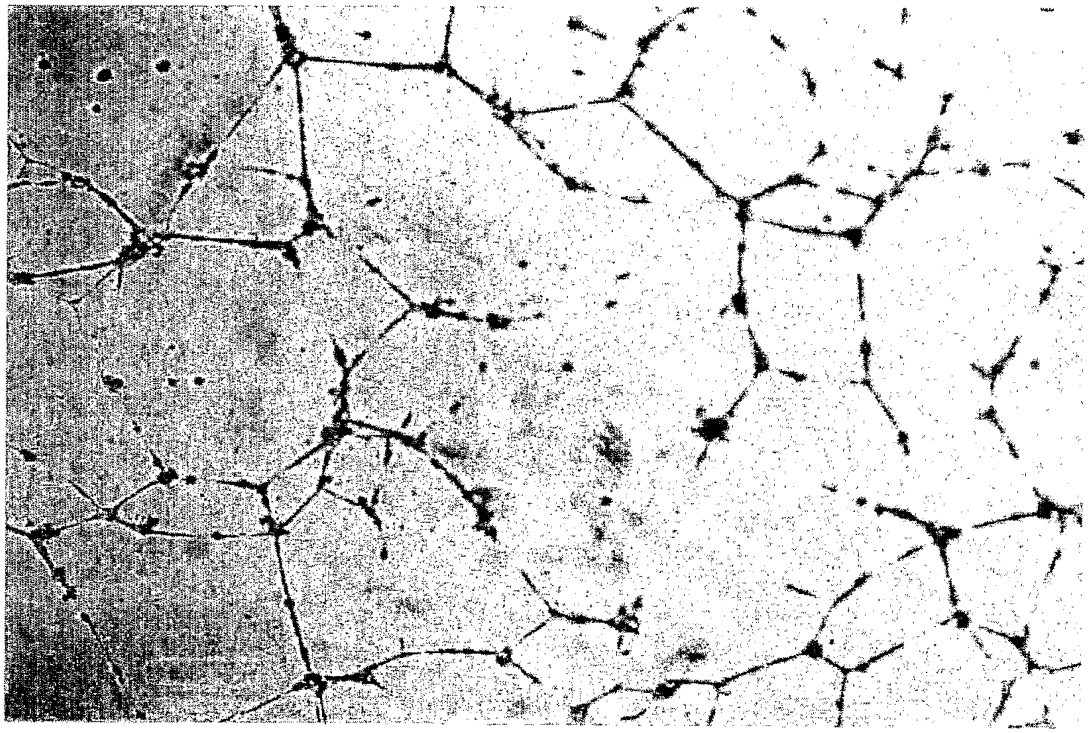
[FIG. 2]



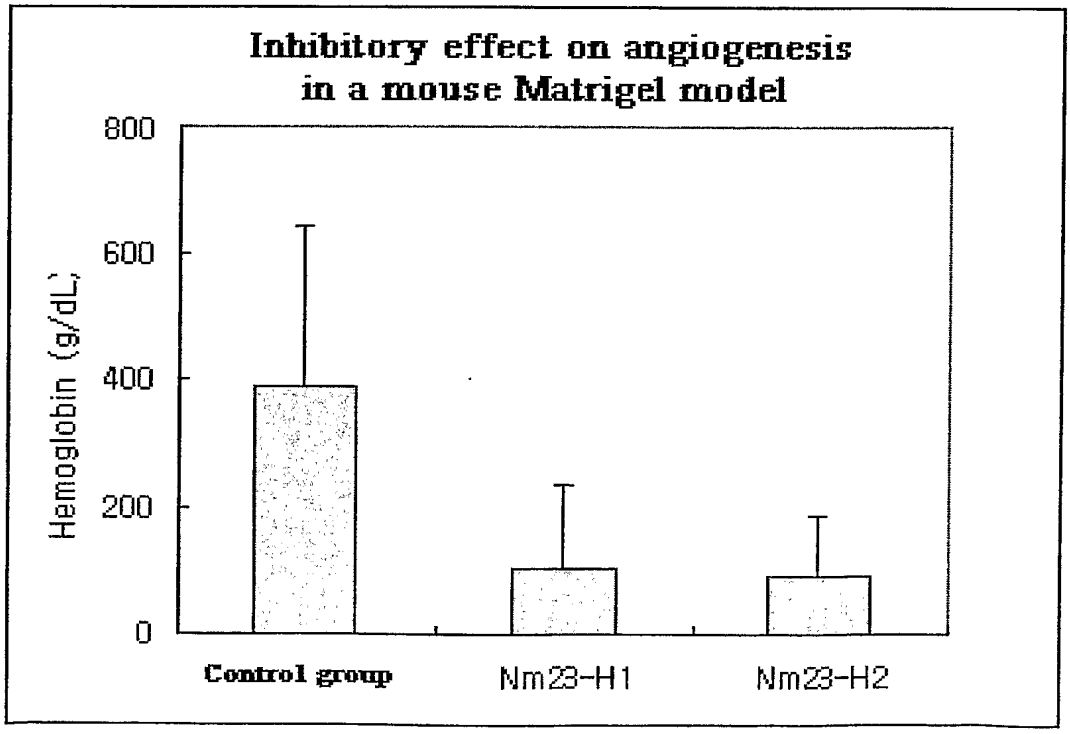
[FIG. 3]



[FIG. 4]



[FIG. 5]


Inhibitory effect on angiogenesis
in a mouse Matrigel model
800
600
400
200
0
Hemoglobin (g/dL)
Control group
Nm23-H1
Nm23-H2

Sequence Listing

<110> ANGIOLAB, INC.
KIM, Min-Young
LEE, Kong-Joo
KIM, Eunhee
PARK, Byung-Young

<120> Compositions comprising Nm23 protein for the use of matrix metalloproteinase inhibitor and angiogenesis inhibitor

<130> 03PP020

<150> KR 10-2002-0011500
<151> 2002-03-05

<160> 3

<170> KopatentIn 1.71

<210> 1
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> No.1 Pro is 2,4-dinitrophenyl Pro.

<400> 1
Pro Leu Ala Leu Trp Ala Arg
1 5

<210> 2
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> No.1 Pro is 2,4-dinitrophenyl Pro.

Sequence Listing

<400> 2
Pro Leu Gly Met Trp Ser Arg
1 5

<210> 3
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> No.1 Pro is 2,4-dinitrophenyl Pro.

<400> 3
Pro Tyr Ala Tyr Trp Met Arg
1 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00419

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 A61K, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KR, JP : IPC as above

Electronic data base consulted during the internationl search (name of data base and, where practicable, search terms used)
PubMed "Nm23", "MMP", "angiogenesis"
NCBI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	LI et al. ' Angiogenesis and the expression of nm23-H(1) tumor metastatic suppressor gene in primary breast carcinoma and their relations to lymph node metastasis' Zhong hua Wai Ke Za Zhi, 2002 Mar, Vol.40(3), p.177-9 see abstract	1-5
X, P	see abstract	6-10
Y	GRYCZYNSKI et al. 'Evaluation of CD44 adhesion molecule, nm23 gene product expression and intensity of angiogenesis in patients with laryngeal cancer' Otolaryngol. Pol. 2000, Vol.54(6), p.669-74 see abstract	1-10
A	MOUSA, Angiogenesis Inhibitors and Stimulators: Potential Therapeutic Implications, Texas, USA, 2000 see pages 124 to 133	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 MAY 2003 (12.05.2003)	13 MAY 2003 (13.05.2003)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
LEE, Mi Jeong
Telephone No. 82-42-481-5601